REVIEW ARTICLE ON “PROTECTIVE EFFECTS OF PHYLLANTHUS NIRURI EXTRACT AND IT'S NANOPARTICLES ON DIABETIC NEPHROPATHY IN DRUG-INDUCED DIABETIC RATS”

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ABSTRACT

"Diabetes mellitus", is one of the most common non-communicable diseases worldwide. India faces several challenges in diabetes management, including a rising prevalence in urban and rural areas, lack of disease awareness among the public, limited health care facilities, high cost of treatment, suboptimal glycaemic control and rising prevalence of diabetic complication. Diabetes mellitus (DM) is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. Type 1 DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin, and presently requires the person to inject insulin or wear an insulin pump. This is also termed as "juvenile diabetes". Type 2 DM or non-insulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, a condition in which cells fail to use insulin properly, with or without an absolute insulin deficiency. This type was previously referred to as or "adult-onset diabetes". The third main type is gestational diabetes which occurs when women without a previous history of diabetes develop a high blood glucose level during her pregnancy. It may precede development of type 2 DM. Various herbal drugs have been also proved effective due to their beneficial contents in treatment of diabetes. Phyllanthus niruri traditionally been used in many tropical countries to treat various ailments, such as kidney stones, chronic liver diseases, diabetes and viral infections. The versatile ethnomedicinal usage of the herb is tightly associated with its multiple pharmacological properties such as immunomodulator, anti-viral, antibacterial, diuretic, anti-hyperglycemia and hepatoprotector. The scope of this review is effect of Phyllanthus niruri.
nanoparticles on diabetes. Insulin therapy for diabetes is most commonly delivered via subcutaneous injections, up to four times a day. Long-term insulin therapy, compounded by the invasive nature of its administration, has caused problems with patient compliance, ultimately influencing patient outcomes.

KEYWORDS: Diabetes mellitus, diagnosis, treatment, Phyllanthus niruri.

1 INTRODUCTION
Diabetes mellitus (DM) is commonest endocrine disorder that affects more than 100 million people worldwide (6% population). It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. It is found to damage many of body systems particularly blood vessels, eyes, kidney, heart and nerves.\(^1\) Diabetes mellitus has been classified into two types i.e., insulin dependent diabetes mellitus (IDDM, Type I) and non-insulin dependent diabetes mellitus (NIDDM, Type II). Type I diabetes is an autoimmune disease characterized by a local inflammatory reaction in and around islets that is followed by selective destruction of insulin secreting cells whereas Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion.\(^2\) Diabetes mellitus is a chronic disorder of carbohydrates, fats and protein metabolism. A defective or deficient insulin secretory response, which translates into impaired carbohydrates (glucose) use, is a characteristic feature of diabetes mellitus, as is the resulting hyperglycemias.\(^3\) Phyllanthus sp. is one of the largest genera in the flowering plant belongs to the family Phyllanthaceae. Many trees, herbs and shrubs were described under the genus, approximately more than thousand species were identified and reported in diverse parts of the world including tropical Asia, China, India, Africa, America and Australia. The presence of valuable bioactive components makes the Phyllanthus more popular in the field of pharmacology based on the usage as an herbal drug in Ayurveda, Homeopathy, Naturopathy, Siddha, Unani and Yoga.\(^4\) Usually the entire plant of P. niruri is used in medicinal preparations by herbalists since the active phytochemicals, such as flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins, have been identified from various parts of the plant.\(^5,6\) The plant extract lowers blood glucose by increasing glycogenesis, inhibiting gluconeogenesis in the liver or inhibiting the absorption glucose from the intestine. Insulinotropic properties of T.foenum graecum seeds of hydroalcoholic extract showed improved glucose homeostatic along with effective glycerides control.\(^7\) Compounds present in the extract are responsible for the regeneration of β cells
affecting normal secretion of insulin. Extracts of this herb have been proven to have therapeutic effects in many clinical studies, which will also be presented in this review.[8]

1.1 Nanoparticle
A nanoparticle is a small object that behaves as a whole unit in terms of its transport and properties.

Advantages
- Smaller size
- Higher surface area
- Higher bioavailability
- Can be administered via different routes
- Uniform delivery of drug

Disadvantages
- Very costly formulation
- Low yield
- Reduced ability to adjust the dose
- Highly sophisticated technology
- Production is more difficult

2 DIABETIC NEPHROPATHY
Diabetic kidney disease occurs in patients with diabetes mellitus (DM) and reduced kidney function that can from many diverse causes, including hypertensive nephrosclerosis and unresolved acute kidney failure. Diabetic nephropathy is a diagnosis that refers to specific pathologic structural and functional changes seen in the kidneys of patients with DM (both type 1 and type 2 [T1/T2DM]) that result from the effects of DM on the kidney. These changes result in a clinical presentation that is characterized by proteinuria, hypertension, and progressive reductions to kidney function.[9] In earlier stage, diabetic nephropathy (DN) manifests by renal hyper-perfusion and hypertrophy. The stage starts with the onset of diabetes in T1DM before insulin treatment. This is called stage 1 and is followed few years later by stage 2 characterized by clinical silence and morphologic changes characteristic of diabetic glomerulosclerosis. Glomerular filtration rate (GFR) is still higher than normal during
this stage. Some diabetic patients continue in this stage throughout their live. Increased urine albumin excretion (UAE) was first described by Keen and Chlouverak is in 1963.[10]

The risk of DN is strongly linked to poor glycemic control in both T1DM and T2DM. In addition, there is strong evidence that tight blood sugar control has a significant impact on primary prevention of DN. However, tight glycemic control is not always an easy task.[11]

2.1 Treatment of DN

Treatment to delay DN progressive involves adequate control of metabolic and hemodynamic abnormalities. In practical terms, this means adequate blood glucose lowering and control of hypertension. A description of all glucose lowering agents is beyond the scope of this review but certain agents have theoretical benefits beyond glucose lowering. Certain antihypertensive are also preferred based on studies which have demonstrated reductions in proteinuria or preservation of GFR, or both. Nonpharmacological approaches and alternatives medicine are briefly discussed. There is also interest in novel agents, gene therapy, and stem cell treatment, which may someday find a place in the treatment armamentarium.[12]

2.2 Methods of Diabetic Nephropathy

2.2.1 Streptozotacin induced diabetes

In this method there was twenty four wistar albino rats of 200-250 g each were grouped into 4 groups with six rats in each group (control, diabetic, diabetic treated and standard drug - glibenclamide treated). After treatment for 8 weeks, the animals were sacrificed and the biochemical parameters like serum total protein, albumin band globulin, urea, uric acid and creatinine were measured for the evaluation of kidney damage.[13]

2.2.2 Allaxon model of diabetes mellitus

In this method Thiny five Wistar rats (200-250 g) were divided to 7 groups. The rats received alloxan (1.p.. 200 mg/kg) for induction of diabetes. After one week, fasting blood sugar (FBS) was assessed and the rats with FBS-250 mg/dl. were considered as diabetic. Three weeks after alloxan injection, the blood urea (BUN) and creatinine (Cr) were determined for confirmation of inducing nephropathy. Then, the animals were treated with carvacrol for one week. Finally, they was anesthetized and blood was collected from animal's heart for calculation of BUN and Cr. Furthermore, the kidneys were for oxidative stress markers such as glutathione capacity, protein carbonyl, lipid peroxidation and catalase activity.[14]
3 Plant Profile of Phyllanthus Niruri

3.1 Botanical study

3.1.1 Taxonomical Classification of Phyllanthus Niruri

Table No 01: Taxonomical Classification of Phyllanthus Niruri.

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Plantac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division</td>
<td>Magnoliophyta</td>
</tr>
<tr>
<td>Class</td>
<td>Magnoliopsida</td>
</tr>
<tr>
<td>Order</td>
<td>Euphorbiales</td>
</tr>
<tr>
<td>Family</td>
<td>Euphorbiales</td>
</tr>
<tr>
<td>Genus</td>
<td>Phyllanthus</td>
</tr>
<tr>
<td>Species</td>
<td>Niruri</td>
</tr>
</tbody>
</table>

3.1.2 Vernacular Names: In India

Table No. 02. Vernacular Names in India.

<table>
<thead>
<tr>
<th>Marathi</th>
<th>Rayavali, Bhuivali</th>
<th>Sanskrit</th>
<th>Amla, Vitunika, Bhumyamalaki</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hindi</td>
<td>Chalmeri, Harfarauri, Bhuianola</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kannada</td>
<td>Kirunelli, Nalla Nelli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Konkani</td>
<td>Bhuin-avalac</td>
<td></td>
<td></td>
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<tr>
<td>Telugu</td>
<td>Ratsavusirike, Nela Usiri</td>
<td></td>
<td></td>
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<tr>
<td>Tamil</td>
<td>Arunelli, Keela Nelli</td>
<td></td>
<td></td>
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<tr>
<td>Oria</td>
<td>Narakoli</td>
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</tbody>
</table>

3.1.3 Phytochemical Studies

Table No. 03. Phytochemical studies.

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>4-methoxy-nor-securinine, Nirunine, ent-norsecurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banzenoid</td>
<td>Gallic Acid, Corilagin</td>
</tr>
<tr>
<td>Coumarin</td>
<td>Ellagic Acid, ethyl brevifolin carboxylate</td>
</tr>
<tr>
<td>Flavonoid</td>
<td>Quercetin, rutin, astragalin, quercitrin, isoquercitrin, kaempferol-4-rhamnopyranoside, eridictyol-7-rhamnopyranoside, fisetin-4-O-glucoside</td>
</tr>
<tr>
<td>Lignin</td>
<td>Phyllanthin, Hypophyllanthin, niranthin, nertetralin, phyltetralin, hinokinin</td>
</tr>
<tr>
<td>Lipid</td>
<td>Ricinoleic acid</td>
</tr>
<tr>
<td>Phytallate</td>
<td>Phyllester</td>
</tr>
<tr>
<td>Sterol</td>
<td>Estradiol, β-sitosterol, isoprpyl-2-4-cholestrol</td>
</tr>
<tr>
<td>Tannin</td>
<td>Geranin</td>
</tr>
<tr>
<td>Triterpene</td>
<td>Lupeol acetate, lupeol, phyllanthenone, phyllantheol</td>
</tr>
</tbody>
</table>

4 MATERIALS AND METHODS

4.1 MATERIALS

- Collection of plants materials (Phyllanthus Niruri)
- Authentication of plant
- Extraction of plant materials with suitable solvent
• Preparation of silver nanoparticles from that extract.

4.2 Preparation of Extraction

4.2.1 Aqueous extraction
The arial plant material was air dried until complete dryness, after dry powdering using mechanical grinder. 45g of P. niruri was soaked in 1050ml of distilled water in a beaker. The mixture was shaken and allowed to stand for 24 hours before filtering with a cheese cloth. The filtrate was evaporated using an oven at 50-60°C. Appropriate weights of the residue were prepared in distilled water to obtain the various concentrations used for the experiment.\[15\]

4.2.2 Methanolic extraction
The 500g of P. niruri powdered were extracted with the help of Soxhlet apparatus with 1.5 liter methanol (80%) as a solvent. The extract was dried and refrigerated at 40°C for further usage.\[16\]

4.3 METHODOLOGY

4.3.1 Experimental work
Diabetes was induced in rats by a single intraperitoneal (IP) injection of freshly prepared solution of alloxan monohydrate (100 mg/kg).
After 48 hours of alloxan injection blood was drawn from retro-orbital of anesthetized rats and glucose content was estimated. Only those rats with blood glucose above 250 mg/dl were selected for study.
Evaluation of anti-diabetic activity of plant extracts and silver nanoparticles on that plant extracts. Drug induced diabetes models were used for the evaluation of anti-diabetic activity.

Animals will be divided in to different treatment group like
• Normal control: 4 rats
• Diabetic control: 4 rats
• Standard drug treated Group: 4 rats
• Extract treated Group: 4 rats
• Nanoparticles treated group: 4 rats

Parameters will be evaluated
• Blood glucose levels
Urea
Serum albumin
Serum creatinine
Serum total protein
Body weight
Urine volume

5 CONCLUSION
In present research work an effort was made to examine protective role of Phyllanthus niruri in the treatment of diabetic induce nephropathy.

On the basis of the extensive literature survey and findings of present study revealed that Phyllanthus niruri is an impotent medicinal plant with various chemical constituent and it possesses pharmacological activities like antihypertensive, antidiabetic, hypolipidemic, anti-inflammatory etc. which also helpful for protective action in diabetic nephropathy.

The finding of the present study suggest that both methanolic and aq. extract of P. niruri significantly decreases blood glucose level in allaxon induce diabetic rats as well as protect kidney from damage due to diabetes by significantly increases the level of albumin and total protein and significantly decreases level of uric acid, urea and creatinine in serum in diabetic induce rat.

Such result clearly indicates that P. niruri methanolic and aq. extract both having the pharmacological activities that exhibits nephroprotective effect against alloxan induced diabetic rats, which may be attributed to the synergistic action of various active compounds present in this plant extract like alkaloid, steroids, glycoside, terpenoids, flavonoids phenolic compound, tannin, coumarins, saponins, phytallate and lignans etc. which has been clearly demonstrated biochemically.

By considering these finding it can be conclude that methanolic and aq. extract of Phyllanthus niruri areal pat proves its role to protect against diabetic nephropathy in rats. Further study required to evaluate exact mechanism of action of both the extract of Phyllanthus niruri.
REFERENCE

